REMARKS

Claims 22-30 were pending. Claim 23 has been canceled. Claim 24 has been amended to eliminate dependency to canceled claim 23. Claims 22 and 30 have been amended to more particularly point out and distinctly claim the invention. Support for amended claims 22 and 30 can be found, *e.g.*, on page 7, lines 8-11; page 17, line 33 to page 18, line 23; page 24, lines 20-27; page 81, lines 29-30; and page 82, lines 19-21 of the instant specification. As such, the claim amendments do not introduce new matter. Claims 31-35 have been added to more particularly point out and distinctly claim the invention. Support for new claims 31-35 can be found, in addition to the disclosure supporting amended claims 22 and 30 above, on page 30, lines 18-23; page 25, lines 18-22; and page 27, lines 8-29 of the instant specification.

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application. Upon entry of the present amendments, claims 22-35 will be pending and under active consideration.

The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 22-28 are rejected under 35 U.S.C. § 102(b) as anticipated by Nakanishi et al. (Internal Medicine 1998, 37:519-522; hereinafter "Nakanishi"). The Office Action states that Nakanishi discloses a case report of an HBV-positive woman whose HBV DNA levels decreased following combination treatment of cyclosporin plus interferon alpha (INF-α). The Office Action notes that Nakanishi does not teach that cyclosporin reduces cytosolic calcium levels, or that cyclosporin interferes with mitochondrial calcium channel activity; however, the Examiner suggests that, as cyclosporin was used in Nakanishi, all claims to use of a calcium modulator for treatment of HBV infection are anticipated. Applicants emphatically disagree and submit that Nakanishi does not anticipate the claimed invention, and thus, the rejection under 35 U.S.C. § 102(b) should be withdrawn, for the following reasons.

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989) (holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim").

Nakanishi teaches that treatment of a single HBV-positive patient with combination therapy of INF-α, glycyrrhizin, and cyclosporin resulted in decreased HBV DNA levels (page 521, Figure 1). Treatment of HBV with combination therapy of INF-α, glycyrrhizin, and cyclosporin, in this case, resulted in decreased HBV replication, but there is no suggestion, much less any teaching, in Nakanishi that cyclosporin treatment alone would produce a similar result. Nakanishi does not teach treatment of HBV-infected patients with cyclosporin as the sole antiviral agent. Applicants point the Examiner's attention to amended claim 22 and new claims 31-35, which claim methods of treating HBV infection that comprise administration of a calcium modulator as the only antiviral agent, or administration of a calcium modulator in combination with an antiviral agent other than INF-α. Nakanishi does not teach a method for treating HBV infection or inhibiting HBV virus replication that comprises administration of a compound that modulates the level of cytosolic calcium as the only antiviral agent. At most, Nakanishi teaches that combination therapy that includes cyclosporin was used in treatment of one HBV-positive patient.

Nakanishi does not anticipate the claimed invention. As the Examiner admits, Nakanishi does not teach that cyclosporin reduces cytosolic calcium levels, or that cyclosporin interferes with mitochondrial calcium channel activity. Nor does it teach that cyclosporin alone is effective for treating HBV infection. The instant application provides methods of treatment of HBV infection utilizing a calcium modulator (see *e.g.*, Section 5.2.2) or a calcium modulator in combination with another therapeutic agent (see *e.g.*, Section 5.2.4). Nakanishi does not teach or suggest using any other calcium chelator, such as BAPTA or BAPTA-AM, nor does Nakanishi teach or suggest an *in vitro* assay to find a compound useful for the treatment of HBV that comprises contacting a cell expressing the HBV protein HBx with a compound and determining whether cytosolic calcium levels are altered due to the presence of the compound. These aspects of the invention as claimed are taught in the instant specification, and are not anticipated by Nakanishi.

In view of the foregoing, Applicants submit that Nakanishi does not anticipate the claimed invention, and the rejection under 35 U.S.C. § 102(b) should be withdrawn.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 22-30 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. As Applicants discuss below, claims 20-30, and new claims 31-35 are enabled by the specification as filed, and the rejection of claims 20-30 cannot be maintained.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See Northern Telecom, *Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation.").

The Examiner acknowledges that the instant specification enables the treatment of a cell line *in vitro* with calcium chelators or calcium modulators to inhibit HBx-mediated activation of Src family tyrosine kinases such as Pyk2. However, the Examiner contends that these data do not enable the use of the claimed methods *in vivo* using any or all agents that can modulate cytosolic calcium *in vitro*. Applicants respectfully disagree. In order, however, to more clearly point out and distinctly claim certain embodiments of the present invention, and to advance prosecution of the current application, while in no way acquiescing with this rejection, Applicants have amended independent claims 22, 29, and 30, (and all claims dependent thereon) to recite a method for treating HBV-infected patients using cytosolic calcium modulators that are shown by *in vitro* methods to inhibit activation of the Src family tyrosine kinase Pyk2. Applicants submit that the instant specification provides an enabling disclosure for use of calcium modulators shown to affect Pyk2 activation *in vitro* for the treatment of HBV *in vivo*.

The instant application discloses the inventors' discovery that Pyk2 activity and cytosolic calcium are essential for HBV infection, and that compounds that inhibit Pyk2 and/or cytosolic calcium can inhibit HBV DNA replication. The data in the specification demonstrate that HBx protein is required for HBV replication (see, *e.g.*, page 21, lines 22-23, Section 7.2 on pages 70-73, and page 78, line 12 to page 79, line 2), that HBx induces

Pyk2 activity (see, *e.g.*, page 79, line 28 to page 80, line 9), and that HBx activation of Pyk2 increases HBV DNA replication (see, *e.g.*, page 82, lines 25-27). The specification further demonstrates that HBx-mediated activation of Pyk2 requires cytosolic calcium (see, *e.g.*, page 80, line 19 to page 81, line 9 and page 82, lines 1-24), and that compounds that modulate the levels of cytosolic calcium (*e.g.*, EGTA, BAPTA-AM, and Cyclosporin A) inhibit HBx stimulation of Pyk2 and prevent HBx-mediated activation of HBV DNA replication (see, *e.g.*, page 80, line 26 to page 81, line 6 and page 82, lines 5-7 and 21-23). The specification describes methods of treating HBV infection by modulating cytosolic calcium levels and also discloses methods to determine effective dosages for therapeutic treatments (see *e.g.*, Section 5.4.3). Based on these data combined with the detailed teaching of the specification, one of skill in the art would recognize that HBV replication could be effectively inhibited by inhibiting HBx action using compounds that modulate cytosolic calcium levels, calcium channels, or Pyk2 activity. The specification further provides various modalities of treatment using known available compounds. One skilled in the art could readily determine dosages and routes of administration using the teachings in the specification (see *e.g.*, Section 5.4.3) to practice the claimed methods of the invention.

The Examiner appears to require that the *in vitro* data be corroborated by experiments utilizing an animal model. However, in the instant case, the art based model for studying HBV replication is a cell-based model (see, *e.g.*, Section 5.5.1 of the present specification). Applicants remind the Examiner that if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate (see M.P.E.P. § 2164.02, Feb. 2003 revision of original 8th ed.).

In the instant case, the relevant art is that related to human hepatitis B virus. At the time of the invention, none of the animal systems suggested by the Examiner (woodchuck, murine, and duck) were universally accepted as animal models of HBV disease. Instead, cell-based assays were used as more reliable predictions of efficacy for treating HBV infection. Applicants draw the Examiner's attention to Sprinzl *et al.*, 2001, J. Virol. 75:5108-5118 ("Sprinzl"), which was previously offered for the Examiners' consideration with the Applicants' Amendment filed October 21, 2003. As noted in that Amendment, Sprinzl describes HBV cell cultures as an art recognized method to study HBV infection. Sprinzl further relates the inadequacy of the animal models available at the time of filing. Thus, the art related to HBV at the time of the invention recognized such cell-based assays as an accepted model for HBV replication because animal models were

not readily available (*see*, *e.g.*, Sprinzl, column 2 at page 5108). As such, one skilled in the art related to the invention would recognize a cell-based assay as being a reasonably predictive model for HBV replication. Thus, the Applicants have utilized an art accepted model to demonstrate the effectiveness of the claimed methods of using compounds that modulate cytosolic calcium and/or Pyk2 activity for the reduction of HBV replication.

Applicants emphasize that 35 U.S.C. § 112 does not require *in vivo* testing of the methods encompassed by the claims. In particular, the Federal Circuit has deemed results of *in vitro* tests sufficient as long as they are reasonably correlated with, without being absolutely predictive of, a pharmacologically useful *in vivo* response. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 USPQ2d 1895, 1899 (Fed. Cir. 1996).

Applicants submit that the *in vitro* studies provided in the examples of the instant specification, combined with the teachings in the specification for treatment of HBV in patients, enable the use of the claimed methods of using calcium modulators for treatment of HBV *in vivo*. The specification provides data showing that treatment of HBV-infected cells with calcium modulators reduces HBV DNA replication. The specification further teaches use of compounds that modulate cellular calcium, such as cyclosporin, for the treatment of HBV in patient populations. The effective doses of cyclosporin taught in the specification are within clinically acceptable and safe ranges. In particular, the specification shows that 1μg/ml of cyclosporin is effective to inhibit HBV replication in cells (see page 82, lines 1-9 of the instant specification as amended, and Figure 10). To achieve therapeutic efficacy, the specification recommends administering cyclosporin to patients in amounts that will achieve such inhibitory plasma levels (see page 46, lines 6-16 of the instant specification). Using ordinary skill, a practicing physician can readily determine the dose required to achieve plasma levels of 1μg/ml. Therefore, Applicants respectfully submit that Examiner's contention that *in vitro* studies cannot be extrapolated to *in vivo* methods of treatment as disclosed in the present application is incorrect, and cannot be used as a basis for a lack of enablement rejection.

The Examiner further contends that treatment of HBV-infected patients with cyclosporin is unpredictable. The Examiner cites Lau, et al. (Lau, et al., Transplantation, 1989, 53:894-898, hereinafter "Lau"), Sandrini, et al. (Sandrini, et al., Nephrol. Dial. Transplant., 1990, 5:525-530, hereinafter "Sandrini"), and Nakanishi, et al. (Nakanishi, et al., Internal Medicine, 1998, 37:519-522, hereinafter "Nakanishi") in support of the unpredictability of cyclosporin in HBV-infected patients. The Examiner cites Lau and Sandrini as evidence that cyclosporin treatment increases HBV DNA replication in HBV-

positive patients, and cites Nakanishi as evidence that cyclosporin treatment decreases DNA replication in HBV-positive patients. However, in contrast to the Examiner's allegations, neither Lau nor Sandrini teach that cyclosporin increases HBV DNA replication, and while Nakanishi does provide evidence of a decrease in HBV DNA replication following cyclosporin treatment, the treatment in Nakanishi involves combination therapy and not treatment with cyclosporin alone.

Lau teaches that treatment with cyclosporin does not affect expression of HBV surface antigen (HBsAg) in hepatocytes cultured from HBV-positive patients. The studies in Lau were performed to determine the effect of immunosuppressive drugs, such as cyclosporin, on HBV antigen presentation by hepatocytes, under short-term (18 hour) cell culture conditions. The results in Lau indicate that cyclosporin treatment of HBV-positive liver cells neither increases nor decreases HBsAg expression in these cells under these conditions. There is no mention of HBV DNA replication in relation to the data presented for cyclosporin treatment. The Examiner points to Table 3 on page 283; it appears that the Examiner intended to draw attention to Table 4 of page 897, which depicts the effect of cyclosporin on HBsAg expression. This table shows only HBsAg expression, not HBV DNA levels. As stated in Lau in relation to the data presented in Table 4, "cyclosporin had no effect on intracellular or secreted HBsAg" (page 896, second column, last paragraph). Lau does not detail any effect of cyclosporin on HBV DNA replication, and concludes only that under the short term culture conditions of the study, cyclosporin had "no immediate direct effect on HBV" (page 898, first column, first paragraph). Lau does not teach that cyclosporin increases or decreases HBV replication. Therefore, the Examiner's citation of Lau in support of the unpredictability of cyclosporin treatment for modulation of HBV replication is in error and cannot support the rejection.

Sandrini details a study of 14 HBsAg-positive renal transplant patients treated with cyclosporin and steroids. The Examiner points to the abstract of this reference as evidence that treatment of HBV-positive patients with cyclosporin increases HBV DNA replication. However, the abstract makes no statement that cyclosporin increases HBV replication, nor is such a statement found anywhere in Sandrini. The abstract states that 11 of the 14 transplant patients treated with cyclosporine and steroids developed hepatitis, where six of the 11 cases of hepatitis were HBV-related and five were not HBV-related (page 525, abstract, first paragraph). This statement does not indicate that cyclosporin increases HBV replication. The abstract then summarizes the results of the study as indicating that, in part, there is a high possibility of non-HBV-related hepatitis in HBV-

positive transplant patients treated with cyclosporin (abstract, page 525, third paragraph). This statement also does not indicate that cyclosporin increases HBV replication. These are the only references to cyclosporin in the abstract, and there is no suggestion that cyclosporin treatment has any effect on HBV replication. A reading of the entire reference fails to find support for the Examiner's contention. Sandrini indicates that the patients in the six HBV-related cases of hepatitis tested serum-positive for HBV DNA (page 527, Table 2), while the five non-HBV-related cases of hepatitis tested serum-negative for HBV DNA (page 527, Table 3). This data provides no more than evidence of the presence or absence of HBV in the serum of patients; Sandrini does not correlate HBV DNA serum levels to HBV replication in any way. Sandrini does not teach that cyclosporin increases or decreases HBV replication. Therefore, the Examiner's citation of Sandrini in support of the unpredictability of cyclosporin treatment for modulation of HBV replication is in error and should be removed.

Nakanishi teaches that treatment of a single HBV-positive patient with combination therapy of interferon alpha (INF-α), glycyrrhizin, and cyclosporin resulted in decreased HBV DNA levels (page 521, Figure 1). However, Nakanishi does not provide evidence that cyclosporin is responsible for the decrease in DNA levels, and the data presented indicate that HBV DNA levels continued to decline following termination of cyclosporin treatment but with continued treatment using INF-α and glycyrrhizin (page 521, Figure 1; the Figure indicates that cyclosporin treatment was terminated in February 1997, but HBV DNA levels continued to decline through April 1997, from 5.4 MEq/ml to <0.7 MEq/ml), suggesting that INF-α and glycyrrhizin were the key treatments relevant to reduction on HBV DNA levels. Treatment of HBV with combination therapy of INF-α, glycyrrhizin, and cyclosporin, in this case, resulted in decreased HBV replication, but there is no teaching or conclusion that cyclosporin treatment alone would produce a similar result. The Examiner's allegation, based on the teachings of Lau, Sandrini, and Nakanishi, that cyclosporin treatment for HBV-positive patients produces conflicting results relating to HBV replication, cannot stand and must be withdrawn.

A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971); In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Here the Examiner can point to no such reason.

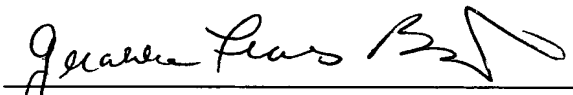
One skilled in the art would, in view of the detailed teaching of the specification, understand such teaching and be able to use the presently taught method for treating HBV-infected patients as claimed. Accordingly, the rejection of the present claims based on Section 112, first paragraph, cannot stand and must be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered and made of record in the file history of the present application. Withdrawal of the Examiner's rejections and a notice of allowance are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: August 2, 2004



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